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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/230,929 | 04/02/1999 | JURGEN KLEINSCHMIDT | 4121-107 | 3634 |

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| EXAMINER | |
|---|---|
| WOITACH, JOSEPH T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | 24 |

DATE MAILED: 06/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/230,929 | KLEINSCHMIDT ET AL. | |
| | Examiner | Art Unit | |
| | Joseph Woitach | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 April 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *14-61,65 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-61,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 4, 2002, paper number 22, has been entered.

**DETAILED ACTION**

This application is a 371 national stage filing of PCT/DE97/01629, filed July 30, 1997, which claims benefit to foreign application 196 31 357.0 filed August 2, 1996 in Germany.

As indicated in the request for continued examination Applicants' after final amendment February 4, 2002, paper number 19 (copy entered as paper number 21), has been entered. Claims 62-64 have been canceled. Claims 14, 49, 50-53, 61 and 65 have been amended. Additionally, Applicants' amendment filed April 4, 2002, paper number 23, has been received and entered. Claims 14, 49-53, 61 and 65 have been amended. Claims 14-61, 65 and 66 are pending and currently under examination.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-25, 27-30, 32, 34, 36, 38, 40, 42-60, 65 and 66 rejected under 35 U.S.C. 103(a) as being unpatentable over Donnelly *et al.* and Johnson is withdrawn.

As noted in the Advisory action mailed February 12, 2002, paper number 20, Examiner agrees that while Donnelly *et al.* and Johnson teach the expression of multivalent antigens of both early and late ORFs of papillomavirus, neither reference provides the specific teaching to combine the various proteins, or fragments thereof, into one fusion protein comprising both an early ORF and a late ORF. Lacking the specific teaching to combine the proteins into one fusion protein, the teachings of Donnelly *et al.* and Johnson do not make obvious the instantly claimed invention, and the rejection is withdrawn.

Claims 14-61, 65 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson (WO 96/00583), Donnelly *et al.* (5,658,785) and Whittle *et al.* (5,955,087).

Claims 14 and 49-53 are drawn to an AAV vector comprising a polynucleotide sequences which encodes a fusion protein, wherein said fusion protein comprises at least a fragment of a late ORF encoding a structural papillomavirus and at least a fragment of an early ORF which is non-transforming. Dependent claims and specific alternative combinations recited in the independent claims are drawn to specific early and late ORFs and specific high risk HPVs. Claims 65 and 66 are drawn to methods of activating an immune system of a subject using the papillomavirus DNA vaccine. At the time of filing Johnson teaches that a recombinant adeno-associated virus (AAV) is useful for DNA delivery to cells. More specifically, Johnson teaches that sequences of interest can be inserted into AAV vectors for use as DNA vaccines (columns 3-5). Johnson provides working examples of the expression of viral proteins in mammalian cells demonstrating the usefulness of the AAV vectors for the production of viral antigens. Johnson provides the detailed teaching for the use of the AAV vector as a DNA vaccine for the delivery and expression of viral proteins in a mammalian cell, however the references does not provide the necessary sequences and information regarding the papillomavirus. At the time of filing Donnelly *et al.* describe the use of DNA vaccines for papillomavirus. Donnelly *et al.* teaches generally that any appropriate vector can be used for delivery and provide a detailed teachings regarding the papillomavirus ORF sequences, and the use and delivery of various combinations of the ORFs in DNA vaccines for papillomavirus. More specifically, Donnelly *et al.* teach that

an effective vaccine encodes combinations of multiple antigenic epitopes comprising any of the ORFs of the papillomavirus (for example page 12; lines 9-11). By example Donnelly *et al.* provide specific fusion proteins for use as a vaccine, however the reference does not specifically teach every combination of early and late ORFs for use as a vaccine (see for example Example 7, page 24). Whittle *et al.* teach that at the time of filing many of the ORFs have been used for the production of HPV vaccines (see columns 1-3), and provide specific and necessary guidance to generate polynucleotide sequences which encode fusion proteins comprising late and early ORFs of papillomavirus. In summary, Johnson teaches that AAV vectors are useful delivery vectors for DNA vaccines for specific virus and known viral antigens, and Donnelly *et al.* and Whittle *et al.* provide the necessary sequences and guidance for the production of papillomavirus vaccines. Therefore, in view of the teachings of the references as a whole, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate a DNA vaccine as generally taught by Donnelly *et al.* using the specific AAV vectors of Johnson to deliver the HPV fusion proteins as taught by Whittle *et al.* Each reference provides a detailed teaching of the particular invention described therein, however requires additional details to practice the full scope of the invention. For example, Johnson provides the AAV vector and motivation for use in DNA vaccine but does not provide the specific antigenic sequences, Donnelly *et al.* and Whittle *et al.* provide polynucleotide sequences for papillomavirus vaccines but does not provide a detailed teaching of delivery vectors. One having ordinary skill in the art would have been motivated to combine the particular teachings of each of the instant references

in order to affect the common goal of generating a DNA vaccine, and in particular a vaccine to papillomavirus. At the time of filing Donnelly *et al.* and Whittle *et al.* each teach that papillomavirus sequences were effective in generating a prophylactic immune response to particular papillomavirus antigens in a subject, and Johnson teaches that the AAV vectors were effective in infecting a wide range of mammalian cells and expressing a specific viral antigen (see for example Example 6), therefore, there would have been a reasonable expectation of success given the successful results of Johnson, Donnelly *et al.* and Whittle *et al.* to insert the specific papillomavirus sequences taught by Donnelly *et al.* and Whittle *et al.* into the AAV vector of Johnson and using said vectors to induce an immune response in a subject.

With regard to arguments presented in Applicants' after final amendment, Applicants have argued that Examiner has failed to establish a *prima facie* case to combine the teachings of each of the references. Further, Examiner has not explained with any specificity what areas of the reference would suggest the combination of the references, citing *Ex parte Humphreys* in support of their argument. See Applicants after final amendment (paper number 21) pages 7-8. It is noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant case, Applicants arguments are not found convincing because the combination of the

references is provided by the teachings of the references as a whole. First, it is noted that each references pertain to analogous art regarding vaccines. Second, as set forth in detail above, each reference provides detailed teachings of the particular invention described relying the teachings known in the art to provide more detailed information for use of the specific invention. Donnelly *et al.* teach a papillomavirus DNA vaccine and Whittle *et al.* teach more specific chimeric protein sequences for use in a papillomavirus vaccine. Donnelly *et al.* teach that any appropriate vector can be used for delivery, and Johnson is relied upon for the specific teaching that AAV vectors were known and used in the art for the delivery of DNA vaccines. At the time of filing, clearly polynucleotide sequences for the papillomavirus were known and used for generating vaccines, clearly DNA vaccines for papillomavirus were known, and clearly AAV vectors were used as specific vectors for the delivery of DNA vaccines. The specific motivation to one of ordinary skill in the art to combine the references is provided by the reliance of the teachings of the art that each reference requires.

Therefore, absent evidence to the contrary, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 16, 18, 20 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson, Donnelly *et al.* and Whittle *et al.* as applied to claims 14-60, 65 and 66 above, in further view of Gissmann *et al.* (WO 96/11272).

Claims 16, 18, 20 and 50 are dependent claims which recite and encompass the use of specific high risk HPV. Briefly, the combined teachings of Johnson, Donnelly *et al.* and Whittle *et al.* make obvious an AAV vector comprising a polynucleotide sequences which encodes a fusion protein, wherein said fusion protein comprises at least a fragment of a late ORF encoding a structural papillomavirus and at least a fragment of an early ORF which is non-transforming. The teachings of the combined references provide for the use of HPV in general, however none of the reference specifically teach all the strains of HPV recited in claims 16, 18, 20 and 50. Gissmann *et al.* teach fusion proteins comprising early and late ORFs of the papilloma virus. In particular, Gissmann *et al.* teach HPV 16, 18, 33, 35, and 45 (page 13, lines 29-36) and the use of the early and late ORFs from these HPV for their use in vaccines. At the time of filing known papillomavirus vaccines comprised antigens from various HPV in order to provide a more protective effect, therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the specific teachings of Gissmann *et al.* providing fusion proteins of early and late ORF from various strains into the papilloma DNA vaccine taught by Johnson, Donnelly *et al.* and Whittle *et al.* One having ordinary skill in the art would have been motivated to substitute use these particular strains of HPV for use in vaccines because they represented papillomavirus which were known in the art to be associated as high risk HPV. There would have been a reasonable expectation of success given the level of skill in the art to substitute the sequences taught by Gissmann *et al.* into the DNA vaccine taught by Johnson, Donnelly *et al.* and Whittle *et al.* Further, given the specific HPV comprised known

antigens there would have been a reasonable expectation that the use of said vectors to express the particular proteins and to induce an immune response in a subject.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson, Donnelly *et al.* and Whittle *et al.* as applied to claims 14-61, 65 and 66 above, in further view of Stanley *et al.* (6,096,869).

Claim 61 is a dependent claim directed to a composition comprising one or more immune system-activating agents. It is noted that the recombinant AAV vector alone would constitute one immune system activating agent, and the basis of the instant rejection focuses on the addition of more than one agent. Johnson, Donnelly *et al.* and Whittle *et al.* have been summarized above. The teachings of the combined references provide for the use of an AAV vector encoding early and late ORFs, however none of the references specifically teach to add other agents to the composition. Stanley *et al.* teach a composition comprising polynucleotide sequences encoding HPV sequences and the addition of IL-12 or a functional homologue (see for example claim 5). The specification teaches that administration of IL-12 and HPV sequences results in the regression of HPV induced tumors (column 2; lines 47-50). Stanley *et al.* provides general teaching for the administration of the polynucleotide encoding HPV antigens, however they do not teach the specific vectors which are necessary for providing the correct expression levels of said proteins. Therefore, it would have been *prima facie* obvious to one having

ordinary skill in the art at the time the invention was made to add IL-12 as a vaccine adjuvant as taught by Stanley *et al.* with the papilloma DNA vaccine taught by Johnson, Donnelly *et al.* and Whittle *et al.* to provide for a more effective composition. One having ordinary skill in the art would have been motivated to add IL-12 in light of the unexpected highly efficient finding of Stanley *et al.* for the significant increase in effectiveness for the composition. There would have been a reasonable expectation of success given the level of skill in the art to add IL-12 to the composition comprising the DNA vaccine taught by Johnson, Donnelly *et al.* and Whittle *et al.* and provide a composition which would be effective in inducing an immune response in a subject.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gissmann *et al.* US Patent 6,228,368.

Edwards *et al.* US Patent 6,306,397.

Bruck *et al.* US Patent 6,342,224.

Hallek *et al.* US Patent 6,352,696.

Each of the above references provides further evidence that at the time of filing polynucleotide sequences of the papillomavirus were used to generate fusion proteins for use in vaccines. It is noted that none of the references specifically teach to deliver the sequences as an

AAV vector DNA vaccine, however as in Whittle *et al.* provides detailed guidance and evidence for providing various combinations of early and late ORF papillomavirus sequences as vaccines.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach

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